

### **Remarks**

This paper amends claims 1, 9-11, 30, 37-39, cancels claims 18-29, and adds new claims 46-56. After the amendments set forth above are entered, claims 1-4, 6-17, 30-45 are pending and claims 1-4, 6-17, and 46-56 are under examination.

Claims 1, 9-11, 30, 37-39 are amended to replace “oxo” acid with “keto” acid. As is well known in the art, a keto acid is a carboxylic acid further comprising a ketone functional group. Support for the amendment is found at ¶ 6 which discloses oxo organic acids that contain a keto group (keto acid), and at ¶ 56 and Table 7 which provides examples of keto acids. Claims 1 and 30 are amended to specify that the oxygen-18-labeled acid may be glyoxylic acid. Support for this amendment is found at the first entry of Table 7. Claims 1 and 30 are amended to include that the oxygen-18-labeled acid may be an hydroxyl mono-acid of Table 1 except wherein said hydroxyl mono-acid is not homovanillic acid. Support for this amendment is found in Table 1 and ¶ 7 of the Specification. Support for new claims 46-53 is found generally throughout the Specification and in the claims from which they depend. Support for new claims 54-56 is found in the Specification at ¶ 11.

### **Request for rejoinder of claims**

In the previous Office Action mailed March 18, 2008, the Examiner restricted claims 1-45 into four groups. In response to the restriction requirement the Applicant has elected Group I (claims 1-4, 6-17) drawn to a method of measuring the amount of unlabeled organic acid in a sample. Group IV (claim 30-45) are drawn to a method of diagnosing an individual with a metabolic defect characterized by an abnormal amount of an unlabeled organic acid in a sample of the individual using the method of the inventions of Group I. The Examiner has acknowledged the inventions of Group I and Group IV are related as combination and sub combination. Office Action mailed March 18, 2008, at p. 2. Applicant respectfully submits that examining inventions of Group IV (claims 30-45) will not require different field of search and thus will not be any additional burden on the Examiner. Accordingly, no savings of PTO

resources will be realized by maintaining the restriction as originally set forth. Applicant therefore requests the rejoinder of the inventions of Group I and IV.

**Rejection of claims under 35 U.S.C. § 102(b)**

Claims 1-4 and 6-17 stand rejected as allegedly being anticipated by Ikegawa et al. (Analytical Sciences (1999), 15: 625-31). Applicant respectfully traverses this rejection.

In order to anticipate a claim, a single prior art reference must provide each and every element set forth in that claim. In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). See also, MPEP §2131. The Examiner bears the initial burden of establishing a *prima facie* case of anticipation.

**Rejection of claims 1-4 and 6-8**

As examined, claim 1 encompassed a method of measuring the amount of an unlabeled organic acid in a sample, comprising adding to the sample an amount of a standard comprising one or more oxygen-18-labeled organic acids selected from the group consisting of dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate, and oxo acid. The Examiner alleges Ikegawa et al. anticipates claims 1-4 and 6-8 by the use of an oxygen-18-labeled oxo organic acid. Applicant respectfully traverses this rejection.

Ikegawa et al. measure a variety of bile acid glucuronides in human urine using mass spectrometry. Ikegawa et al. use a oxygen-18-labeled 24-glucuronide benzyl ester-benzyl ether derivative of chenodeoxycholic acid ("24-G CA") as an internal standard. 24-G CA is generally a mono-carboxylic acid, but further comprises five hydroxyl groups (three on the glucuronide moiety and two on the chenodeoxycholic acid moiety). This multi-hydroxy mono acid does not fall within the scope of claim 1 and therefore cannot anticipate the currently amended claims. Accordingly, this rejection is traversed and should be withdrawn.

Rejection of claims 9-17

Amended claim 9 encompassed a method of measuring the amount of an unlabeled organic acid in a sample, comprising adding to the sample an amount of a standard comprising one or more oxygen-18-labeled organic acids selected from each of dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate, and keto acid. The Examiner alleges Ikegawa et al. anticipates claims 9-17. Applicant respectfully traverses this rejection.

Applicant respectfully points out that claim 9 and its dependent claims require that the standard contain at least one oxygen-18 labeled organic from each of acid classes of hydroxyl mono acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate, and keto acid. Thus, the standard must contain at least seven oxygen-18-labeled organic acids.

The Examiner alleges that Ikegawa et al. discloses three or more oxygen-18-labeled organic acids from oxo acids added to a urine sample. Office Action at page 3, referring to Tables 1-3 of Ikegawa et al. Applicant respectfully disagrees.

Contrary to the Examiner's allegation, there is no evidence that any of the bile acids detected in the Tables 1-3 were oxygen-18-labeled. Ikegawa et al. describes the data in Table 1 by stating:

Known amounts of 24-glucuronides were added to the urine of a healthy volunteer and their recoveries were estimated (Fig. 7). As listed in Table 1, all the bile acid 24-glucuronides used exhibited satisfactory recoveries.

Ikegawa et al., p. 629, right column.

The data in Table 2 quantifies the amount of 24-glucuronides in the urine of healthy volunteers. Ikegawa et al., p. 629, right column. There is no evidence that any exogenous organic acids were added to the urine samples in this case. Table 3 provides a ratio of fragment

ion to deprotonated molecule in “authentic samples” and urine samples. In no case does Ikegawa et al. suggest that any of the measured 24-glucuronides are oxygen-18-labeled. At most, it may be inferred that the oxygen-18-labeled chenodeoxycholic acid standard was added to aid in the quantification; however, even this point is unclear. It is possible that the quantification was done in the absence of an oxygen-18-labeled standard.

Even if each of the 24-glucuronides identified in Table 1 of Ikegawa et al. were oxygen-18-labeled (which Applicant strongly urges has not been proven), each sample would contain, at most five labeled compounds belonging to a single class of organic acid. This falls far short of the standards of claim 9 which require at least seven oxygen-18-labeled organic acids, drawn from at least seven different classes. Furthermore, all five 24-glucuronides are mono carboxylic acids which do not fall within any of the acid classes specified in claim 9.

For the foregoing reasons, Applicants respectfully submit that this rejection is traversed and should be withdrawn.

### **CONCLUSION**

Applicant believes that the present application is now in condition for allowance. Prompt and favorable action on the application is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of

papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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